REMARKS/ARGUMENTS

I. Amendments

Claims 16-24 and 26-41 are pending and stand rejected. Claims 1-15 and 25 were previously canceled. With entry of this Amendment, Applicants have canceled previously pending claims 16-41 and have added new claims 42-74. Support for new claims 42-74 can be found in the specification as originally filed, the claims as originally filed and the claims as previously pending and, thus, no new matter has been added. Applicants respectfully request reconsideration of the pending claims in view of Applicants' amendments and accompanying arguments.

II. Response to Claim Rejections under 35 U.S.C. § 112, paragraph 1

A. Summary of rejections in the Office Action

On page 2 of the Office Action, the Examiner rejected claims 16-24, 26-31, 33, 35, 38 and 40 as "failing to comply with the enablement requirement." Claims 32, 34, 36-37, 39 and 41 were rejected under 35 U.S.C. § 112 because, according to the Examiner, the specification failed to "reasonably provide enablement for [the claimed methods when] practiced *in vivo*." See Office Action at page 10. The Examiner suggested that claims 32, 34, 36-37, 39 and 41 would be allowed if limited to *in vitro* applications.

The Examiner's arguments presented in the Office Action may be summarized as follows. First, the Examiner reads Applicants' claims more broadly than they would be read by one skilled in the art. Second, to establish the state of the art and the level of skill in the art, the Examiner improperly relies on sensational news articles written in the aftermath of several widely-publicized tragedies. Finally, the Examiner implicitly and improperly requires Applicants to present clinical data sufficient to garner FDA approval of the claimed methods.

Applicants address these issues in detail below and provide arguments which, Applicants respectfully submit, show that the claims have been improperly rejected.[1] Applicants also note that, in addition to the arguments presented herein, the pending claims have been substantially amended in order to facilitate prosecution and move the claims towards allowance. Applicants expressly reserve the right to pursue claims of equal or greater scope in a related application.

B. Regarding the vector used in the clinical trials described in Applicants' declaration

On page 6 of the Office Action, the Examiner notes that "the specific adenoviral vector used in the articles (rAD-p53 SCH 58500) is not disclosed in the instant application." Applicants submit that the vector rAD-p53 SCH 58500 is an A/C/N/53 vector as described in Applicants' specification and recited in Applicant's claims. As described in Nielsen et al. (*Cancer Research, 59*:5896-5901 (1999) (copy enclosed)), this delivery vector is a human wild-type p53 adenovirus, also referred to as SCH 58500, p53 Ad, rAd-p53, or ACN53 (*see, id.* at page 5897). Thus, the specific adenoviral vector used in the articles is disclosed in Applicants' application.

C. Applicants do not claim a method of curing cancer without any of the risks associated with FDA-approved cancer therapies

Before passing on the allowability of claims under any section of 35 U.S.C., an Examiner is first required to give the claims their "broadest reasonable interpretation." *See* MPEP § 2111. In the Office Action, however, the Examiner evaluates Applicants' claims as if the claims were drawn to methods of *curing* cancer or eliminating tumors without any of the risks associated with FDA-approved cancer therapies. For example, the Examiner alleges on page 3 that the specification fails to address the "art recognized hurdles to *successful* practicing

[1] Applicants and Examiner discussed several of the issues raised herein during a brief telephonic Interview on February, 2004. Applicants greatly appreciate the thoughtful comments provided by the Examiner and the Examiner's generous donation of his time. Agreement was not reached, however, with respect to the allowability of the pending claims.

of gene therapy for treatment of cancer." The Examiner then cites from a list of articles which, taken together, stand for the incontrovertible proposition that gene therapy is not a magic bullet.

Whether "gene therapy" is correctly construed to encompass only (or even primarily) methods of eliminating tumors from patients in the absence of side effects is moot. Applicants have canceled their claims which explicitly recited the term "gene therapy." Generally speaking, Applicants' pending claims are drawn to a method of *inhibiting or reducing* the growth or proliferation of tumor cells, *in vivo* and *in vitro*, using a specified and novel replication-deficient recombinant adenovirus. Many of Applicants' pending claims include additional limitations. Insofar as Applicants do not claim to have invented "gene therapy," Applicants submit that they need not prove that they have enabled "gene therapy." Moreover, as stated in MPEP 2164.08, the scope of enablement need only bear a "reasonable correlation" to the scope of the claims. *See, e.g., In re Fisher*, 427 F.2d 833, 839 (CCPA 1970); *see also Atlas Powder Co. v. E.I. Du Pont De Nemours & Co.*, 750 F.2d 1569, 1576 (Fed. Cir. 1984) (a claim may encompass inoperative embodiments and still meet the enablement requirement). It is respectfully submitted that the methods described in Applicants' disclosure bear a reasonable correlation to the methods recited in the amended claims. Therefore, particularly in light of the clinical data presented in Applicants' Response to the previous Office Action and discussed further below, Applicants respectfully submit that the pending claims satisfy the enablement requirement.

D. The references cited in the Office Action do not accurately reflect the state of the relevant art or the skill of those in the relevant art

1. *Wands* factors, predictabilty, and the state of the art

The Federal Circuit has addressed the factual premises of the enablement analysis for biological processes, explaining that determination of whether the requisite amount of experimentation is undue may include consideration of:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those

> in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

See In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). With respect to the level of skill in the art, Applicants take issue with the Examiner's assertion that, at the time Applicants filed their application, the "relative skill of the artisans in the gene therapy art was (is) very low." *See* Office Action at page 8. As discussed above, Applicants do not claim to have invented "gene therapy", nor do Applicants contend that the scope of their claims includes the universe of "gene therapy" procedures. Applicants contend that the relevant art to consider is the art of administering recombinant adenoviruses to targeted cells *in vivo* such that the adenoviruses are incorporated into the targeted cells and expression of genes encoded by the adenoviruses is observed. At the time of Applicants' filing, there were many highly skilled practitioners capable of following Applicants' disclosed protocols and performing the routine experimentation -- manipulation of virus titers, identification of tumor cells likely to be targetable, *etc.* -- required to successfully practice Applicants' claimed methods.

For example, as early as 1994, effective peritumoral delivery of adenoviruses encoding p53 was demonstrated by Wills et al. (*Human Gene Therapy, 5*:1079, 1081 (1994)) (copy enclosed). Also, Schuler et al., in *Human Gene Therapy, 9*:2075-2082 (1998) (copy enclosed) report the successful intratumoral administration (*see, e.g.*, p. 2077) of adenoviruses expressing heterologous genes, and Nielsen et al. *supra* (p. 5897) provide examples of effective intraperitoneal administration.

The determination of cells that are deficient in p53 activity is also routine. For example, Wills et al. (1994) *supra* discuss p53 detection at page 1081. Thus, the necessary techniques were known to the artisan at the time the present application was filed and undue experimentation would not be necessary to evaluate the status of p53 in tumor cells in order to practice the presently claimed invention.

Additional references showing that only routine experimentation, if any, would be necessary to practice Applicants' claimed method is presented in the discussion which follows relating to the art cited by the Examiner.

2. The references cited by the Examiner are not representative of the state of the art

As stated above, the Examiner cites the opinions of several individuals that "gene therapy" has not yet entered mainstream clinical practice. The Examiner also cites several news stories describing some severe side effects that have arisen during the course of administration of DNA-based therapies to morbidly diseased patients. Generally speaking, these articles represent the opinions of a handful of authors and are not absolutes. Moreover, the articles speak to the clinical and commercial success of a broadly defined "gene therapy" paradigm; they do not address the likelihood that, in light of Applicants' detailed disclosure, Applicants' narrowly claimed methods could be practiced by those skilled in the art without undue experimentation.

a) Gomez-Navarro et al.

On pages 3-4 of the Office Action, the Examiner cites passages from an article by Gomez-Navarro which allegedly suggest the unpredictability and ineffectiveness of any therapeutic methods which utilize recombinant gene expression (pages 3-4).

However, the last paragraph of the Introduction to the article, on page 868, shows that the authors intend to describe only how "gene therapy" had not evolved to become a routine clinically "accepted" cure-all:

> In the treatment of human malignant tumours, several obstacles explain the limitations of currently available treatments for achieving *definitive cures* in most cases of advanced disease. It is apparent that [current non-recombinogenic technologies] *can achieve incremental improvements in cancer treatment.* But these therapies . . . probably will not bring the much-needed *radical advances* in the implementation and results of cancer treatment. In contrast, gene therapy offers the potential for overcoming some of these *fundamental barriers.* (emphasis added)

In another passage cited by the Examiner, relating to mutation compensation, Gomez-Navarro likewise speculates that "nearly every tumour cell *might* have to be targeted for these approaches to be *clinically effective.*" (page 871, emphasis added) With respect to the Applicants' pending method claims, Gomez-Navarro clearly does not suggest that every cell in a

tumor *must* be targeted to achieve *any* diminishment in the rate of division of *any* cell in a tumor comprising a defective tumor suppressor gene.

Thus, the Examiner (like Gomez-Navarro) sets up a straw man where enablement of a claim depends on proof of clinical "success" in the art of "gene therapy," and "success" is recognized, apparently, only when methods of treating cancer with an adenoviral vector are proven to be *de facto* commercially viable (*i.e.*, when all three phases of a clinical trial are successfully completed).

Applicants also note that Gomez-Navarro summarize on page 871 various apoptotic vectors, but do not discredit the vectors disclosed in Applicants' application. Applicants' novel vectors exemplify some of the myriad improvements ("breakthrough developments") on the pathway to "successful" adenovirus vector-based "gene therapy" alluded to in the article.

Finally, Applicants respectfully wish to draw the Examiner's attention to an apparent contradiction. As noted above, the Examiner cites the Gomez-Navarro article as support for the "art-recognized hurdles" to gene therapy. Interestingly, in spite of the Examiner's characterization of the article, one of the authors of the article, David T. Curiel, filed a patent application in 1997 with claims reciting methods for transducing cells with replication-deficient adenoviral vectors. The purpose of the methods as stated in the specification of Dr. Curiel's patent is to allow "effective genetic correction in the context of gene therapy." The patent (U.S. Patent No. 6,333,030) issued Christmas Day, 2001. The Examples provided in Dr. Curiel's patent specification describe the transduction of a xenografted tumor in mice. Dr. Curiel did not provide any clinical data in the patent specification or by declaration during prosecution.

Applicants have presented claims at least as narrowly drawn as those issued to Dr. Curiel and have included clinical data showing the successful delivery and expression of their vector in humans. Applicants are confused by the seemingly contradictory stance taken by Dr. Curiel and the Examiner with respect to the efficacy, predictability and enablement of "gene therapy" claims. Applicants submit that the pro-"gene therapy" position Dr. Curiel took under

oath before the PTO is more credible than any view he might have expressed in a journal article intended merely for the titillation of its readers.

b) The Fox article

The article by freelance science journalist Richard Fox, cited by the Examiner at pages 5-6, was published in the wake of the widely publicized death of Jesse Gelsinger during the course of clinical trials evaluating the safety of a gene therapy protocol utilizing an adenovirus vector. The treatment was intended to correct an extremely rare and severe disease caused by the lack of a gene encoding an essential metabolic gene, ornithine transcarbamylase. This sort of gene therapy is strikingly different in kind from that taught and claimed by Applicant. Applicant teaches, in contrast, the correction of a tumorigenic defect in a tumor suppressor gene by recombinantly expressing a tumor suppressor gene, such as p53, or a suicide gene, in the cells of the tumor. In other words, rather than propose a "cure" for a severe systemic disease caused by the absence of an essential metabolic gene, Applicants instead teach a method for decreasing rates of cell division and tumor growth by administering a tumor suppressor gene to the site of the tumor itself.

Furthermore, Gelsinger's death garnered an exceptional amount of negative press because of his young age and because his death occurred immediately and dramatically after administration of the recombinant virus. However, as the Fox article points out, Gelsinger appeared to have been improperly selected for the study and might not have died had proper protocols been followed. In that regard, Fox notes in the article that the remaining 20 or so other participants in the trial developed only "moderately adverse symptoms." The University of Pennsylvania researchers who carried out the trials, including Prof. James Wilson (quoted in the Fox article), ultimately settled out of court. The terms of the settlement were confidential, but the evidence suggests that Dr. Wilson's subsequent "public opinions" regarding gene therapy were dictated to some degree by legal considerations.

On the other hand, Gelsinger's death did not appear to have a great impact on Dr. Wilson's willingness to continue to represent to the PTO that adenovirus-based gene therapy was

safe and effective.[2] For example, the specification of one patent in which Dr. Wilson appears as an inventor states:

> The efficacy of this system in delivering a therapeutic transgene in vivo that complements a genetic imbalance has been demonstrated in animal models of various disorders. Indeed, a recombinant replication defective adenovirus encoding a cDNA for the cystic fibrosis transmembrane regulator (CFTR) has been approved for use in at least two human CF clinical trials. *Further support of the safety of recombinant adenoviruses for gene therapy is the extensive experience of live adenovirus vaccines in human populations.* (Citations omitted; emphasis added)

See U.S. Patent No. 6,203,975.[3] In summary, Applicants submit that the Fox article does *not* fairly represent the views of those skilled in the art with respect to Applicants' claimed methods, just as it does not accurately represent the views of the researchers quoted in the article.

c) The Marshall article

The Examiner cites the Marshall article on page 9 of the Office Action as documentation of the fact that

> clinical retroviral based gene therapy trials have been suspended in the U.S. because of the adverse effects (development of a leukemia disease in patients) resulting from infection by the recombinant retroviral vector.

The Marshall article chronicles the discovery of leukemia in children receiving retroviral gene therapy for X-linked severe combined immunodeficiency (X-SCID). Applicants submit that the Marshall article, like the Fox article, does not show that those skilled in the art of developing recombinant adenovirus treatments for cancer cannot reasonably predict whether a particular construct will have any effectiveness in a clinical setting. Rather, the articles demonstrate only that treating certain particularly severe *genetic diseases* with the retroviral-based or adenovirus-based protocols described in the articles is accompanied by serious risks.

Applicants remind the Examiner that *nearly all* existing methods of treating tumors with pharmaceuticals are accompanied by the risk of serious, often life-shortening, side-effects. To the extent the absence of any risk is neither explicitly nor implicitly included in the

[2] Dr. Wilson appears as the Inventor on approximately 41 "gene therapy"-related patents issued by the PTO.
[3] The patent issued *more than a year* after the Gelsinger incident.

pending claims, the Examiner's heavy reliance on such risks to reject the pending claims is misplaced and contrary to law. *See, e.g., Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994) ("Testing for full safety and effectiveness . . . is more properly left to the [FDA].").

Finally, Applicants note that the FDA's requirements for "safety" and suitable predictability is often higher than that deemed acceptable to scientists and medical practitioners seeking to treat terminally ill people who have no other alternatives. *See, e.g.,* Bailey, R., *ReasonOnline*, "Timid Bureaucrats Kill People," (Jan. 9, 2002) (copy attached).

d) W. French Anderson article

On page 9 of the Office Action, the Examiner refers to a statement made by W. French Anderson, "the foremost gene therapy practitioner," to the effect that "no successful gene therapy protocol had been unambiguously demonstrated" as late as 1998.

Once again, Dr. Anderson's opinions in science journal editorials are strikingly at odds with the positions he took before the PTO with respect to applications in which he appears as an inventor.[4] For example, Dr. Anderson appears as an inventor on U.S. Patent No. 6,503,501, which claims priority to an application filed November 9, 1992. The patent issued January 7, 2003, *after* the death of Gelsinger and *after* the discovery of leukemia in X-SCIDS patients in retrovirus-treated patients. The issued method claims appear to encompass the use of retroviruses for *in vivo* "gene therapy" and, in fact, the specification of the patent clearly states that "an object of the present invention to provide gene therapy by introduction of a vector particle, such as, for example, a retroviral vector particle, directly into a desired target cell of a patient." The specification does not disclose a single Example of *in vivo* efficacy. Nowhere in the patent (and presumably nowhere in the prosecution history) does Dr. Anderson candidly disparage the field of gene therapy as he allegedly does in the *Nature* article cited by the Examiner.[5] Applicants submit once again that Dr. Anderson's statements and actions before the

[4] Dr. Anderson appears as an inventor on at least ten issued gene therapy patents, at least several of which claim priority to applications filed before Applicants' application.

[5] Applicants note that under 37 CFR 1.56 Dr. Anderson had a duty to disclose information *believed to be* material to the patentability of the invention, including information regarding the unpredictability of the art.

PTO are more relevant to his beliefs with respect to the enablement issues at hand than are Dr. Anderson's statements in a journal article summarizing the clinical and commercial "success" of "gene therapy."

e) The Gura article

On page 4 of the Office Action, the Examiner cites the Gura article for the proposition that positive results with cancer therapeutics achieved using animal and/or xenograft models are not predictive enough to enable the treatment of humans, at least for 35 U.S.C. § 112 purposes. As an initial matter, Applicants note that Dr. Oliff, quoted as saying that "[animal] model systems are not predictive at all," continues to regularly direct and publish animal experiments evaluating cancer treatments using xenograft models (a list of seven such articles is attached). Applicants also refer the Examiner to their discussion of the Gomez-Navarro and Curiel patent, above. Dr. Curiel's implicit acknowledgement that xenografted tumors are useful for predicting adenovirus-based treatments in humans is consistent with Applicants' views (and apparently was shared by the Patent Office as well, at least as recently as Christmas Day, 2001).

Furthermore, in Chapter 42 of Cancer Medicine e.5 (B.C. Decker, 5th ed. (2000)), authored by Drs. Samir Khleif and Gregory Curt, entitled, "Animal Models in Developmental Therapeutics." On page 577, Drs. Khleif and Curt state:

> In fact, *excellent correlations can be made between average growth delay for human tumors in nude mice treated with the best available drug combinations and complete clinical response rates*. In increasing order of responsiveness, these correlations have been shown for human xenografts of non-small cell lung cancer, colon cancer, breast cancer, and malignant melanoma. (Citations omitted; emphasis added).

Applicants have attached a copy of this reference for the Examiner's convenience.

In summary, the Examiner's choice of references does not reflect the widespread belief among those skilled in the art that the use of a *xenograft-proven* recombinant adenovirus is *reasonably* likely to effectively diminish the growth of some transfected tumor cells in humans. Applicants' respectfully submit that to satisfy the enablement requirement they need not prove that the risk-free elimination of every tumor type may be achieved using their methods.

Applicants submit that this is particularly true where their claims are drawn so as not to encompass the therapeutic treatment of every known tumor cell type by the universe of adenovirus-derived vectors.

E. Clinical data is unnecessary to show enablement of treatment method claims

For the record, Applicants remind the Examiner that they need ***not*** demonstrate the FDA-required degree of clinical efficacy or even any clinical efficacy at all to meet the enablement requirement. *See In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). The clinical certainty required to treat a human subject is *not* the standard for an enabling disclosure.[6]

Nevertheless, Applicants provide additional evidence that the expression of p53 in humans is not recognized by those of skill in the art as a useless and dangerous exercise. For example, Nielsen et al. in *Cancer Gene Therapy, 5(1)*:52-63 (1998) (copy enclosed) note that several studies report expression of p53 (see, e.g., p. 54) and little or no detrimental treatment-related effects (see, *e.g.*, p. 59). Likewise, Schuler et al. (1998) *supra* report expression of p53 RNA and only mild to moderate toxicity (see, *e.g.*, pp. 2077-2078). Moreover, Reid et al. in *Cancer Gene Therapy, 9*:979-986 (2002) (copy enclosed) note that several studies report p53 expression with an acceptable toxicity profile, including human trials (*see, e.g.*, abstract).

F. The data described in Applicants' specification and Applicants' declaration are sufficient to show enablement of Applicants' claims

Applicants respectfully disagree with several statements made by the Examiner on pages 6-7 of the Office Action. The statements relate to the clinical trials which were described in Applicants' previous Response (filed May 28, 2003) and Dr. Maneval's accompanying declaration under 37 CFR § 1.132. Applicants have already addressed (above) the Examiner's concern regarding the identity and nomenclature of the vectors described in the clinical trial papers and in Applicants' specification.

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[6] To quote Supervisory Patent Examiner Karen Hauda, "We DO NOT Require Clinical Data." (emphasis in original) *See,* the USPTO's "Gene Therapy: Overcoming Enablement Rejections" PowerPoint training materials.

The Examiner states on page 6-7 that "some of the studies involve the use of adenoviral vectors and specific chemotherapy treatments which again are not taught in the instant specification." Applicants respectfully disagree. First, the use of chemotherapeutics in conjunction with Applicants' novel adenoviral vectors is explicitly recognized in the specification at, *e.g.*, page 4, lines 29-36, wherein it is stated:

> As with treating p53 deficient tumors, the goal of gene therapy for other tumors is to reinstate control of cellular proliferation. In the case of p53, introduction of a functional gene reinstates cell cycle control allowing for apoptotic cell death induced by therapeutic agents. Similarly, gene therapy is equally applicable to other tumor suppressor genes which can be used either alone or in combination with therapeutic agents to control cell cycle progression of tumor cells and/or induce cell death.

Second, Applicants are not sure which of the papers the Examiner refers to when he says "some of the articles." Each of the papers presents data from trials conducted, at least in part, in the absence of additional chemotherapeutic agents. *See, e.g.,* Wen et al. Abstract ("Subjects were treated with rAd-p53 SCH 58500 alone during Cycle 1").

The Examiner also states that "the dosages of adenoviral vectors recited in some of the articles appear to be higher than what is disclosed in the instant specification." As an initial matter, Applicants respectfully submit that the determination of effective dosages is well within the purview of those skilled in the art. Applicants do not state in their specification that the preferred dosages are the only dosage ranges which may be used and, given that no undue experimentation is required by skilled artisans to determine effective dosages, Applicants' claims should not be limited only to the preferred ranges recited in the specification. Furthermore, because Applicants disclose in their specification a range of "10^8 to about 10^{13}" infectious units, *i.e.*, a range covering "about" five orders of magnitude, an amount of virus within one order of magnitude of the disclosed range is acceptably close to the preferred concentrations.

Finally, the Examiner states that "none of the articles actually demonstrates successful treatment of patients suffering from cancers resulting from defective tumor suppressor genes." Although the Examiner's definition of "success" is stringent, Applicants respectfully disagree. For example, the Wen et al. paper states on page 236 that, "rAd-53 SCH 58500 was at least partially responsible" for the resolution of tumor tissue in subject 52 (who had failed three

prior chemotherapy regiments). Buller et al. reports on page 562 that "SCH 58500 alone at higher does provides a favorable change in CA125 (a tumor antigen)." Kuball et al. similarly report that "evidence for biologic activity of the transgene . . . as determined by expression of the p53 target gene *p21/WAF1*, was found in patients treated at higher dose levels." These results show that Applicants' methods have demonstrated anti-tumor cell activity.

For all of the forgoing reasons, Applicants respectfully submit that the pending claims are fully enabled. Applicants therefore respectfully request withdrawal of the Examiner's rejections under 35 U.S.C. § 112, first paragraph.

III. Obviousness-type double patenting rejections

Claims 16-24 and 26-41 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 16-24 of copending Application No. 09/860,286 (Publication US 2003/0091534).

Upon notification that allowable subject matter is present in the instant case, Applicants will address this issue.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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Attachments (eight)
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